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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/186,869	11/04/1998	KARL W. HASEL	98.429	2377

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	28

DATE MAILED: 09/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/186,869	Hasel et al
Examiner	**Art Unit**
Jeffrey Fredman	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *April 24, 2001 and April 19, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above, claim(s) *37-41, 73, and 74* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-36 and 42-72* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Petition

1. Applicant's petition to have the holding of abandonment withdrawn was granted.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 8, 10-36 and 42-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erlander et al (WO 95/13369) in view of New England Biolabs catalog (page 11) (1993/1994 catalog).

Erlander teaches an improved method for the simultaneous sequence-specific identification of mRNAs in a mRNA population comprising:

(a) preparing double-stranded cDNAs from a mRNA population optionally enriched for Poly A sequences (page 20, lines 8-13) using mixture of 12 anchor primers, the anchor primers each including: (i) a tract of from 7 to 40 T residues; (ii) a site for cleavage by a restriction endonuclease that recognizes more than six bases, the site for cleavage being located to the 5'-side of the tract of T residues; (iii) a stuffer segment of from 4 to 40 nucleotides, the stuffer segment being located to the 5'-side of the site for cleavage by the restriction endonuclease; and (iv) phasing residues -V-N located at the 3' end of each of the anchor primers, wherein V is a deoxyribonucleotide selected from the group consisting of A, C, and G; and N is a deoxyribonucleotide selected from the group consisting of A, C, G, and T, the mixture including anchor primers containing all possibilities for V and N (page 8, lines 18-36),

(b) cleaving the double stranded cDNA population with a two restriction endonucleases, one of which recognizes four nucleotide sequences and one of which cleaves within the anchor region (page 9, lines 1-11),

(c) inserting the double stranded cleaved cDNA from step (b) into a vector in an orientation that is antisense with respect to a bacteriophage-specific promoter within the vector, (page 9, lines 1-11), expressly teaching the use of the pBC SK vector in which the NotI restriction site is more than 15 nucleotides in length from the transcription initiation site of either T3 or T7 (page 22, lines 16-26),

(d) transforming the host cell with the vector in which the cleaved DNA has been inserted to produced vectors containing cloned inserts (page 9, lines 1-11 and page 22, lines 28-36),

(e) generating linearized fragments of the cloned inserts by digestion with at least one restriction endonuclease that is different from the first and second restriction endonucleases but which cleaves within the vector (page 9, lines 12-15 and page 23, line 9 to page 24, line15),

(f) generating a cRNA preparation of antisense cRNA transcripts by incubation of the linearized fragments with a bacteriophage-specific RNA polymerase capable of initiating transcription from the bacteriophage-specific promoter (page 9, lines 16-20),

(g) generating a first strand cDNA by transcribing the cRNA using reverse transcriptase and by dividing the cRNA preparation into sixteen subpools and transcribing first-strand cDNA from each subpool, using a thermostable reverse transcriptase and one of sixteen primers whose 3'-terminus is -N-N, wherein N is one of the four deoxyribonucleotides A, C, G, or T, the primer being at least 15 nucleotides in length, corresponding in sequence to the 3'-end of the bacteriophage-specific promoter, and extending across into at least the first two nucleotides of the cRNA, the mixture including all possibilities for the 3'-terminal two nucleotides; (page 9, lines 21-31),

(h) generating a first set of PCR products by using the product of transcription in each of the sixteen subpools as a template for a polymerase chain reaction with a 3'-primer that corresponds in sequence to a sequence in the vector adjoining the site of insertion of the cDNA sample in the vector and a 5'-primer selected from the group consisting of: (i) the primer from which first-strand cDNA was made for that subpool; (ii) the primer from which the first-strand cDNA was made for that subpool extended at its 3'-terminus by an additional residue -N, where N

can be any of A, C, G, or T; and (iii) the primer used for the synthesis of first-strand cDNA for that subpool extended at its 3'-terminus by two additional residues -N-N, wherein N can be any of A, C, G, or T, to produce polymerase chain reaction amplified fragments; (page 9, line 32 to page 10, line 10),

(j) resolving the polymerase chain reaction amplified fragments by electrophoresis to display bands representing the 3'-ends of mRNAs present in the sample (page 10, lines 11-13).

Erlander teaches anchor primers with 18 T residues in the T tract (page 16, line 13). Erlander further teaches stuffers anywhere in the range of 4-40. Erlander expressly teaches the use of the T3 promoter (page 24, lines 16-27).

Erlander expressly teaches associating changes in expression with physiological or pathophysiological change using wildtype and test samples (pages 29-33), including processes mediated by growth factors such as steroids (page 33, line 5), tissues such as CNS tissue (page 31, line 4), or retina (page 30, line 25), or peripheral nervous system (page 31, line 20), skeletal muscle (page 31, line 24) diseases such as Alzheimers (page 30, line 31), or glutamate neurotoxicity (page 31, line 7), aging or long-term potentiation (page 31, line 1).

Erlander expressly teaches using the method to determine the effect of drugs being screened (page 31, lines 11-15) including antidepressants (page 32, line 34), steroids (page 33, line 5).

Erlander expressly teaches correlating relative abundance of mRNA with the signal produced including the use of fluorescent labels (page 38, lines 29-36) as well as a preferenc

use of one gel, but directly suggests that multiple gel should be used where sample number requires (page 27, lines 13-35).

Erlander further teaches eluting a cDNA from the gel, amplifying the eluted cDNA by PCR, cloning the amplified DNA, producing the DNA and sequencing it (page 33, lines 14-23).

Erlander does not teach, but does expressly suggest, three elements of the claims. Erlander suggests step (i), which is a repetition of step (h). Erlander suggests the use of restriction enzymes but does not name each enzyme claimed. Erlander generically describes the sequences required, but does not identify the specific sequences claimed.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to follow the suggestion of Erlander who expressly suggests repeating step (h), stating "The use of successive steps with lengthening primers to survey the cDNAs essentially act like a nested PCR (page 28, lines 19-21)". Erlander further notes "In serial iterations of the subsequent PCR step, in which radioactive label is incorporated into the products for autoradiographic visualization, those pools are further segregated by division into four or sixteen subpools by using progressively longer 5' primers containing three or four nucleotides of the insert (page 28, line 32 to page 29, line 2)". Erlander therefore expressly suggests phasing up to three or four nucleotides (page 29).

Erlander expressly suggests the use of any restriction enzyme, including any routine equivalent, and expressly discusses a variety of different enzymes on pages 21-23. The examiner takes official notice of the fact that each of the enzymes cited in claims 24-36 are well known in

the art enzymes each of which is completely characterized and whose characteristics fall within those taught and required by Erlander and each of which is commercially available in catalogs of restriction enzymes as exemplified by page 11 of the New England biolabs catalog.

With regard to the specific SEQ ID Nos claimed, these sequences appear to simply represent arbitrary selection of sequences. In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (34 USPQ 2d 1210, 1214)."

Since the claimed oligonucleotides simply represent structural and functional homologs of the Erlander sequences, which are sequences which have been identified by the prior art as being useful for indexing method, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

4. Claims 1-4, 8, 10-36 and 42-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erlander et al (WO 95/13369) in view of New England Biolabs catalog (page 11) (1993/1994 catalog) and further in view of Kato et al (EP 735 144 A1).

Erlander in view of NEB catalog teaches the limitations of claims 1, 8, 10-36 and 42-72 as discussed above. Erlander in view of NEB does not teach the use of biotin, streptavidin for cDNA capture.

Kato teaches the use of biotin and streptavidin coated magnetic beads for capture of labeled nucleic acid indexing amplified molecules (figure 1 and page 4, lines 30-40).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize biotin and streptavidin to separate the nucleic acid products as taught by Kato in the method of Erlander in view of NEB catalog since Kato states "By using a class-II restriction enzyme, a class IIS restriction enzyme and 64 biotinylated adaptors in the operations described above, the DNA or cDNA fragments generated by class II and class IIs restriction enzymes can be separated. (Page 5, lines 53-55)." An ordinary practitioner would have been motivated to use the biotin streptavidin system for isolation of nucleic acids in order to easily separate the components using magnetic beads as taught by Kato, and in particular, to easily separate out the restricted DNA as taught by Kato.

5. Claims 1, 5-7, 8, 10-36 and 42-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erlander et al (WO 95/13369) in view of New England Biolabs catalog (page

11) (1993/1994 catalog) and further in view of Noronha et al (PCR Methods Appl (1992) 2:131-136).

Erlander in view of NEB catalog teaches the limitations of claims 1, 8, 10-36 and 42-72 as discussed above. Erlander in view of NEB does not teach the use of phosphorothioate linkages.

Noronha teaches the use of phosphorothioate linkages in PCR in order to prevent primer degradation (abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize phosphorothioate linkages as taught by Noronha in the method of Erlander in view of NEB catalog since Noronha states "The data presented here demonstrate that while 3'-5' exonuclease activity can be a hindrance to efficient specific DNA amplification, its activity can be diverted from amplimer degradation and restricted to proofreading through the use of 3' sulfurized amplification amplimers (page 135, column 3)". An ordinary practitioner would have been motivated to combine the use of phosphorothioate oligonucleotides with the method of Erlander in view of NEB catalog in order to reduce background and amplimer degradation.

6. Claims 1, 8-36 and 42-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erlander et al (WO 95/13369) in view of New England Biolabs catalog (page 11) (1993/1994 catalog) and further in view of Ju et al (Anal. Biochem. (1995) 231:131-140).

Erlander in view of NEB catalog teaches the limitations of claims 1, 8, 10-36 and 42-72 as discussed above. Erlander in view of NEB does not teach the use of the specific fluorophores claimed.

The specification admits, on page 13, lines 25-30, that these probes are all known in the prior art.

Ju teaches the use of several of these dyes for DNA analysis (abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the fluorescent dyes of Ju in the method of Erlander in view of NEB catalog because Erlander expressly suggests the use of fluorescent dyes and Ju states "The unique spectroscopic properties of ET primers make them valuable in all areas where high sensitivity and simultaneous spectroscopic discrimination of several fluorescent tags is required (page 140, column 1)". An ordinary practitioner would have been motivated to use the fluorophores of Ju in the method of Erlander in view of NEB catalog for the express motivation of high sensitivity and improved discrimination.

Response to Arguments

7. Applicant's arguments filed originally on April 24, 2001 and refiled April 19, 2002, have been fully considered but they are not persuasive.

Applicant's argue that the rejection of Erlander in view of NEB catalog does not teach the invention. Applicant does not provide specific reasons for this argument. Applicant's arguments amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Consequently, the rejection is maintained.

Applicant then argues that Erlander does not teach ligation of double stranded cDNA adaptors to the double stranded cDNA fragments. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the Erlander, NEB and Kato references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation to combine the Kato reference is provided in the rejection, which notes "An ordinary practitioner would have been motivated to use the biotin streptavidin system for isolation of nucleic acids in order to easily separate the components using magnetic beads as taught by Kato, and in particular, to easily separate out the restricted DNA as taught by Kato."

Applicant relies upon overcoming Erlander in view of NEB to overcome the remaining 103 rejections. Since the Erlander in view of NEB rejection is maintained for the reasons given above, these remaining arguments are not persuasive.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman, Ph.D. whose telephone number is (703) 308-6568.

The examiner is normally in the office between the hours of 6:30 a.m. and 4:00 p.m., and telephone calls either in the morning are most likely to find the examiner in the office.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1637

September 17, 2002